UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

12/DEC/1999

MEMORANDUM

Subject: EPA Reg. No: 65331-U Frontline Plus for Cats
DP Barcodes: D261562
Case No: 066318
PC Code: 129121

From: Masih Hashim, Toxicologist
Technical Review Branch
Registration Division (7505C)

To: Ann Sibold, PM Team 03
Insecticide Branch
Registration Division (7505C)

Applicant: Merial Limited
2100 Ronson Road
Iselin, NJ 08830

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Fipronil	10.0
Methoprene	12.0
Inert Ingredients	78.0
Total:	100.0

BACKGROUND: Merial Limited has submitted a set of five acute toxicity studies (MRID through 449420-04 through 08) to support the registration of its product Front Line Plus for Cats, File Symbol 65331-U. These studies were conducted at the IIT Research Institute (IITRI) at Chicago, IL.

The Registrant requested a waiver for the inhalation study because the product will be used as a spot treatment. The liquid is squeezed out from the tube onto the cat's skin. Respirable particles are not generated, and inhalation exposure in normal use of the product is supposed to be non existent (Registrant's compliance statement 10-1-99) .

RECOMMENDATIONS: Each of the five studies is acceptable in accordance with the Sub-Division F guidelines.

Since the product will be used as a spot treatment and will not have an inhalation exposure (Compliance statement), TRB approves a waiver for the acute inhalation study.

The toxicology profile for the File Symbol 65331-U is as follows:

acute oral toxicity	III	acceptable
acute dermal toxicity	IV	acceptable
acute inhalation toxicity	-	waived
primary eye irritation	IV	acceptable
primary skin irritation	IV	acceptable
dermal sensitization	neg.	acceptable

LABELING:

ID #: 065331-00004 Frontline Plus for Cats

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor.

USER SAFETY RECOMMENDATIOS:

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

Product Manager: 03
MRID No.: 449420-04

EPA Reviewer: M Hashim
Study Completion Date: 9-2-99
Study No.: 1087SN1

Testing Facility: IITRI
Author: John Findlay
Quality Assurance (40 CFR §160.12):
Test Material: ML-2,095,988 508Q
Species: Rats/CD
Age: 50-55 days
Weight: 154-224 gms
Source: Charles River Labs, Portage, Mich.

Conclusion:

1. LD_{50} (mg/kg):
   Males: -
   Females: -
   Combined: > 750 mg/kg
2. The estimated LD_{50} is > 750 mg/kg
3. Tox. Category: III Classification: Acceptable

Procedure (Deviations): Two shipments of rats were used for the same study (not significant)
Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
2.0	4/5	4/5	8/10
1.0	2/5	5/5	7/10
0.5	2/5	1/5	3/10

Observations: Most rats died within 2-3 days following the test article administration. All groups showed hypoactivity, salivation, dyspnea, prostration, coma, and discoloration around mouth and fur.

All surviving animals gained weight during the study.

Necropsy: Surviving animals showed no lesions at necropsy.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200)

Product Manager: 03
MRID No. 449420-05

EPA Reviewer: M Hashim
Study Completion Date: 9-2-99
Study No.: 1087SN2

Testing Facility: IITRI
Author: J. Findlay

Quality Assurance (40 CFR §160.12):

Test Material: ML-2,095,988 508Q
Species: Rats/CD
Weight: 166-223 g
Source: Charles River, Portage, MI

Dermal LD_{50} Testing:

Conclusion:

1. LD_{50} (mg/kg):
   Males: >5000 mg/kg
   Females: >5000 mg/kg
2. Combined LD_{50} is >5000 mg/kg
3. Tox. Category: IV Classification: Acceptable

Procedure (Deviations): None
Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

Observations: Clinical signs were not significant.
Necropsy: Unremarkable.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400)

Product Manager: 03
MRID No.: 449420-06

EPA Reviewer: M Hashim
Study Completion Date: 9-1-99
Study No.: 1087SN4

Testing Facility: IITRI
Author: J. Findlay

Quality Assurance (40 CFR §160.12): Included

Test Material: ML-2,095,988 508Q (Fipronil 9.8%)
Dosage: 0.1 ml
Species: Rabbits; Albino, NZW
Age: 3 months
Weight: 2.0-2.9 kg
Source: Kuiper Rabbit Ranch, Gary, IN
Conclusion:

1. **Toxicity Category:** IV Mild Irritant
2. **Classification:** Acceptable

Procedure (Deviations): None

RESULTS:

Time/Hours	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae				
Chemosis	2/3	0/3	0/3	0/3
Discharge	0/3	0/3	0/3	0/3
Redness	0/3	0/3	0/3	0/3

Summary: An eye irritation score of 5.3 and 2.7 (out of 110) was seen at the one hour and 24 hrs respectively. The irritation subsided within 24 hrs.

DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500)

Product Manager: 04
MRID No.: 449420-07

EPA Reviewer: M Hashim
Study Completion Date: 9-1-99
Study No.: 1087SN3

Testing Facility: IITRI
Author: J. Findlay

Quality Assurance (40 CFR §160.12): Included

Test Material: ML-2,095,988 508Q
Sample Size: 0.5 ml
Species: Rabbit/NZW
Age: 2-3 months
Source: Kuiper Rabbit Ranch, Gary, IN
Conclusion: Mild irritant

1. Toxicity Category: IV
2. Classification: Acceptable

Procedure (Deviations): None
There were 3 animals for this study. Each test site was treated with 0.5 ml of the undiluted test material. Then covered with gauze and secured with a tape for four hrs. After removal of the dressings, observations for dermal irritation and defects were made at 30-60 minutes, 24, 48, 72 hrs and then 7 days in accordance with Draize scoring.

PDIS= 1.75. Slight irritant.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600)

Product Manager: 03
MRID No.: 449420-08

EPA Reviewer: M Hashim
Study Completion Date: 9-3-99
Study No.: 1087SN5

Testing Facility: IITRI
Author: J. Findlay

Quality Assurance (40 CFR §160.12): Included

Test Material: ML-2,095,988 508Q
Positive Control Material: Hexylcinnamaldehyde (HCA) in acetone
Species: Guinea pigs; Albino, Hartley
Wt.: 277-300 g
Source: Charles River, Portage, MI
Method: Buehler

Conclusion: 1. The test substance is not considered a dermal sensitizer.
2. Acceptable

Deviations: None

Procedure: Twenty guinea pigs were topically treated (once weekly) with o.3 ml of undiluted test substance through the induction phase. Two weeks following this phase, the test animals and the naive controls were challenged with 75% w/v test substance (vehicle ML-3, 967,758 000K).

The positive control group (10 animals) received undiluted HCA for induction, and 50% w/v HCA in acetone for the challenge.

Results: At the challenge, only one animal showed minimal reaction in the test group at the This reaction is not considered significant.

There was no reaction within the naive control animals.

Positive control animals showed (appropriate) positive reactions.

ACUTE TOX ONE-LINERS

1. DP BARCODE: D261562
2. PC CODE: 129121
3. CURRENT DATE: 12-14-99
4. Test Substance Fipronil 10% + Methoprene 12%

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/ IITRI/ Rat/ IITRI/ 1087SN1/9-2-99	449420-04	LD_{50} = 750 mg/kg	III	A
acute dermal toxicity/ Rat/ IITRI/ 1087SN2/ 9-2-99	449420-05	LD_{50} > 5000 mg/kg	IV	A
Acute inhalation toxicity/rat/	-	-	-	Waived
Primary eye irritation / Rabbit/ IITRI/ 1087SN4/ 9-1-99	449420-06	mild irritant	IV	A
Primary dermal irritation/ rabbits/IITRI/ 1087SN3/9-1-99	449420-07	mild irritant	IV	A
Dermal sensitization guinea pigs/ IITRI/1087SN5/9-3-99	449420-08	not a dermal sensitizer	-	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated